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Molecular Research Corporation
139 Main Street
Cambridge, Massachusetts

Contract No. AF 19(628)-418
Project No. 6692
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FINAL REPORT

31 March 1963

Prepared for

AIR FORCE CAMBRIDGE RESEARCH LABORATORIES
OFFICE OF AEROSPACE RESEARCH
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FORWARD

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This report covers work performed from March 1962 through February 1963. Participants were Dr. A. S. Obermayer, Project Leader; Dr. L. D. Nichols, Dr. B. E. Norcross, Mrs. C. E. Breed, and Dr. M. Panar. Acknowledgement should also be given to Dr. H. A. Hill and Dr. M. Allen for their stimulating discussions and technical assistance.

ABSTRACT

The synthesis, purification, and characterization of a large number of benzimidazole derivatives are described. Compounds have been prepared which allow for the correlation of systematic structural variations with the physical and electrical properties.

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1. INTRODUCTION

The objective of these investigations has been preparation of a series of closely related high purity benzimidazole derivatives. The electrical properties of these compounds are then to be correlated with molecular properties such as degree of conjugation, electron availability, ring substituents, bond strength, chain length, steric effects and crystal structure. By a comparison of this type, it should be possible to gain considerable understanding about the relationship of chemical structure to electrical conductivity and other physical properties in organic compounds.

This report for the period March 1962 through February 1963 describes the methods of purification and characterization of benzimidazole derivatives to be used for further studies.

2. PREPARATION OF BENZIMIDAZOLES

2.1. Synthesis

In the synthesis program, several methods have been found useful. The majority of these depend upon the reaction of an aromatic (or aliphatic) carboxylic acid -- or one of its esters -- with an aromatic o-diamine.

2.1.1. Direct Acid Synthesis

For aliphatic acids of low melting point, it is usually possible to form the benzimidazoles by heating the diamine for several hours with an excess of the acid at about 100°C (or at the reflux temperature of the acid). This route was utilized for the preparation of 2-t-butylbenzimidazole. The strong trifluoroacetic acid reacts in this fashion with o-phenylenediamine to give an almost quantitative yield of 2-trifluoromethylbenzimidazole. The direct acid synthesis is also useful for preparation of 2-methylbenzimidazoles (acetic acid) and benzimidazoles unsubstituted in the two position (formic acid).[1]

In some instances, the reaction is preferably carried out in 4 N hydrochloric acid and/or with the acid anhydride. This was found to be the case for benzimidazoles made from 3-nitro-o-phenylenediamine (in particular 2-methyl-4-nitrobenzimidazole). 2-Phenyl-4-nitrobenzimidazole can also be made by this means from benzoic anhydride. This reaction is commonly known as the Phillips synthesis.[2]

The benzimidazoles are usually easily separated from the reaction mixture by neutralization of the excess acid, which causes the precipitation of the benzimidazole.

In the case of most aromatic acids the Phillips synthesis fails. It is possible to cause aromatic acids to react by conducting the reaction (in hydrochloric acid) under pressure at 180°-190°C.[2] However, as other procedures exist for the preparation of the benzimidazoles of aromatic acids, pressure reactions have not been attempted in this laboratory.

2.1.2. Polyphosphoric Acid Condensations

Alternative methods for the preparation of 2-arylbenzimidazoles usually involve the use of a high-boiling solvent or dehydrating agent for their success. The formation of the benzimidazole from the starting materials usually becomes an important reaction at about 180°C. The rate of reaction can often be measurably improved by a choice of suitable media and temperatures as high as 290° without causing an untenable increase in the products of side reactions.

One of the most useful media for the condensation is the strongly dehydrating polyphosphoric acid.[3] Condensations carried out in polyphosphoric acid are usually conducted at 180°-250°C under a nitrogen atmosphere and utilize the starting materials in stoichiometric quantities. Reaction times of three to four hours are customary. At the end of the reaction the polyphosphoric acid-benzimidazole mix is partially cooled (to about 50°-150°C) and is poured into ice water, which procedure results in the pre-

cipitation of the benzimidazole. After filtration, the precipitate is washed with water and then treated with dilute base to remove most of the contaminating phosphates and any unreacted carboxylic acid. The benzimidazole is then dissolved out of the precipitate by an appropriate solvent and reprecipitated as a crude product.

Most of the "monomeric" benzimidazoles have been - or can be - prepared by condensation in polyphosphoric acid. There have been notable exceptions, however. In particular, it has not been possible to prepare 2-phenyl-5-nitrobenzimidazole by this method.[4] Difficulties in isolating a product have also been encountered with the following acids:

1. Trans-cinnamic acid (2-styrylbenzimidazole) -- Phosphorylation of the double bond may take place, or possibly isolation of the extremely soluble 2-styrylbenzimidazole formed may be complicated by the large volumes of water involved. Synthesis has been accomplished by the reaction of benzaldehyde with 2-methylbenzimidazole.
2. Pivalic acid (2-t-butylbenzimidazole) -- Violent decarboxylation takes place. Synthesis of this compound has been carried out by the direct acid method.
3. p-Hydroxybenzoic acid (2-p-hydroxyphenylbenzimidazole).
4. p-Methoxybenzoic acid (2-p-methoxyphenylbenzimidazole).

Lack of clear and particular interest in 2-p-hydroxyphenylbenzimidazole and 2-p-methoxyphenylbenzimidazole has prevented further attempts at their synthesis, detailed investigation into the products obtained, or possible reasons for failure.

The polyphosphoric acid method for synthesizing benzimidazoles

has many advantages - the most important of which is that it is literally a "quick and dirty" means of synthesizing a broad range of compounds. However, separating the product from the phosphates present is tedious, and it is also difficult with many of the higher molecular weight materials which have low solubility in even the best organic solvents. In addition, it is not readily applicable for use with amine hydrochlorides because of the foam generated by the evolving hydrogen chloride as the mix is heated. In some of the other methods the hydrochlorides can be used directly.

2.1.3. Ester Synthesis and Variations

It has been found in this laboratory and others that 2-aryl-benzimidazoles can be effectively made by melt condensation of the phenyl esters with o-phenylenediamine (e. g. Ref. 5). Several benzimidazoles, both monomeric and dimeric have been prepared by this method -- among them 2- -naphthylbenzimidazole, 2-m-tolyl-5-methylbenzimidazole, 1,3-bis-(2-benzimidazolyl)benzene and poly-2,2'-(m-phenylene)-5,5'bibenzimidazole. In this laboratory these reactions are usually run at 200°-290°C for two hours. At the end of the reaction, most of the phenol has distilled off and the remainder can be removed by application of a vacuum to the reaction flask. The product is often very easily isolated from the cooled and solidified reaction mixture by leaching with methanol or ether. The unreacted starting materials and impurities will dissolve out leaving the product behind, often in crystalline form.

Several variations of this synthesis have been tried with some success. In the case of 1,4 bis-(2-benzimidazolyl)benzene, the diphenyl terephthalate which would normally be used as a starting material has such a high melting point that the reaction mixture never liquifies. This results in an incomplete reaction and in the production of impurities. If dimethyl terephtlalate is used with phenol as a solvent the reaction proceeds smoothly (T = 250°C) and the product is relatively clean. This reaction is normally run using one mole of phenol for each mole of the acid.

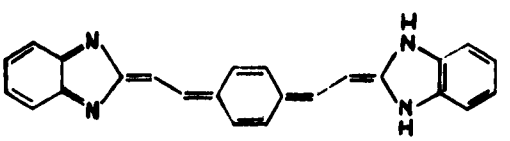
Many aromatic carboxylic acids are not commercially available in the form of their phenyl esters. Although the formation of the phenyl ester from the acid via the acid chloride is relatively straight-forward, it has been found that the benzimidazole will often form from the acid if a stoichiometric amount of phenol is used as a solvent, which obviates the need for making the ester. A small amount of concentrated hydrochloric acid added to the reaction flask seems to catalyze the reaction. In many cases, the phenyl ester produces a cleaner product and is therefore the preferred starting material.

Phenol boils at 182°C and disappears quite rapidly from the reaction mix abcve 200°C. For benzimidazoles melting below 300°C this is not a problem because the reaction mixture usually remains fluid throughout the course of the reaction. For some of the higher melting benzimidazoles, however, the removal of the phenol causes the reaction mix to solidify prematurely, thereby reducing the efficiency and uniformity of heating and resulting in the appearance of more impurities. Accordingly, the use of higher

boiling phenols has been investigated. To date, considerable success has also been obtained with m-cresol(b.p. 204°C). The bis-benzimidazole from β-napthoic acid and 3,3'-diaminobenzidine tetrahydrochloride forms quite readily with m-cresol as a solvent (T = 250°C).

2.1.4. Other Methods

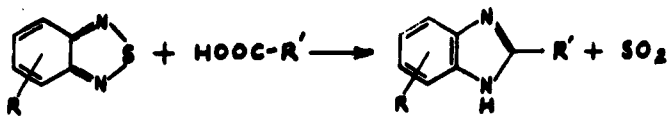
Still another synthetic route recently applied is the condensation of 2-methylbenzimidazole with aromatic aldehydes. Triethyl phosphate has been found to serve as a suitable solvent for this reaction, as do acetic acid and acetic anhydride. Thus, reaction of terephthalaldehyde appears to have provided the interesting compound, $\alpha\beta'$-bis-(2-benzimidazolyl)-1,4-divinylbenzene which may exist as the tautomeric



although characterization of the yellow crystalline product is not complete.

An alternative type of preparative scheme, which has not yet borne fruit, is the attempt to utilize derivatives of o-diamines which can be condensed with carboxylic acids directly. This would allow better purification of starting materials, and would lend itself to more convenient preparation of simple polybenzimidazoles via intermediate acids. A particularly attractive type of compound is piazthiole (2,1,3-benzothiadiazole) prepared from o-phenylene-diamine and thionyl chloride in pyridine. This is a low melting stable crystalline solid which offers a potentially anhydrous

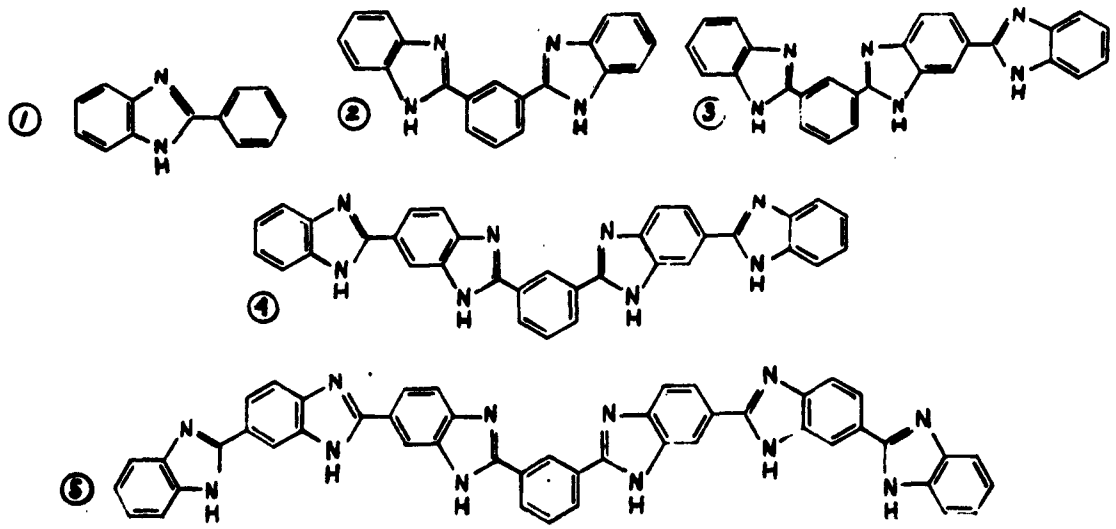
condensation with acids:



Unfortunately, this reaction has not yet proved possible, because of the excessive stability of the piazthiole.

2.1.5. Telemers and Polymers

As a prelude to the study of high molecular weight polymers, a series of telemers of well defined structure and chain length and moderate molecular weight was of interest. In particular, investigation of the following series of benzimidazoles was proposed and synthesis undertaken:



Two procedures were investigated. The first utilized the polyphosphoric acid method for the condensation of 3,4-diaminobenzoic acid in the presence of a considerable excess of carboxylic acid groups in the form of isophthalic acid to form compounds of the type:

which could be further condensed with o-phenylenediamine to give the desired products. A crude separation of the acid products from the first condensation was effected by their differential solubility in alkaline solution. However, the products of the second condensation with o-phenylenediamine proved prohibitively difficult to separate. Therefore, this preparation was postponed until purificational techniques could be more highly developed using simpler benzimidazoles. Column chromatography and high temperature sublimation techniques now in use should simplify product isolation.

A second approach to provide essentially the same series paralleled the work of Porai-Koshits.[6] This utilized the oxidation of ring methyl groups to carboxylic acids. Attempts were made to oxidize 2-m-tolyl-5-methylbenzimidazole to be followed by condensation with o-phenylenediamine or with 3,4-diaminotoluene and a second oxidation. However, it appears that destructive oxidation of the benzimidazole is difficult to avoid under the vigorous oxidation conditions required.[7]

Synthesis of the poly-2,2'-(m-phenylene)-5,5'-bibenzimidazole was accomplished using 3,3'-diaminobenzidine and diphenyl isophthalate according to the method of Marvel and Vogel.[5] This high molecular weight polymer had characteristics distinct from but consistent with the low molecular weight compounds.

2.2. Purification

2.2.1. Preliminary Purification

Benzimidazole crystals involve strong hydrogen bonding and consequent high lattice energies, favoring low intrinsic solubilities. Opposed to this is the low symmetry of most of the compounds, coupled with disorder due to 1(H)⟷3(H) tautomerism. The high degree of ordering required for crystallization of these large molecules manifests itself in slow rates of solid-solute equilibration. Moreover, the solubilities are strongly dependent both on the pH of the solution and the state of the solid phase present. These factors have proven a source of difficulty, but also provide a wide range of conditions which can be profitably manipulated during the course of purification, leading up to sublimation and subsequent efforts toward hyper-purity.

For the lower molecular weight members of the series, recrystallization from methanol and/or acetone has proven to be the easiest method of purification. These are good solvents for treatment with charcoal, but rates of solution are sometimes slow; likewise, the solutions may supersaturate. Precipitation by addition of water to these solvents is relatively non-selective. Slow evaporation often leads to crystallization, but in at least one case 1,3-bis-(2-benzimidazolyl)benzene, the crystals obtained from methanol appear to include this solvent in their crystal structure. Often a combination of both acetone and methanol will improve the rate of solution and the characteristics of the benzimidazole precipitate.

For higher molecular weight materials (most dimers and the trimer from trimesic acid), neither methanol nor acetone dissolves

an appreciable quantity of the benzimidazole. For purification of these compounds, methanolic sodium hydroxide, 6 N aqueous sodium hydroxide, 88% formic acid, and glacial acetic acid have proven to be valuable solvents. Recovery of the benzimidazole is accomplished by neutralization (with CO_2 or dilute HCl) in the case of the sodium hydroxide based solvents. Neutralization must be employed judiciously in the case of formic acid because of the danger of forming gelatinous precipitates. A preferable method for formic acid solutions is dilution with ether or in some cases methanol. Use of ether as the diluent generally favors the formation of a crystalline material. Alternatively, evaporation of formic acid solutions allows isolation of the formate salts.

Aqueous sodium hydroxide is a particularly valuable solvent because it will often separate the benimidazoles from almost all of the impurities. Most of these impurities are highly colored amine condensation products, and formic acid dissolves them quite readily as does any methanol based solvent.

Powerful hydrogen bonding solvents such as dimethyl sulfoxide, dimethylformamide and dimethylacetamide are useful primarily as extractants and lead almost invariably to gelatinous, intractable precipitates. The exceptions are terephthalic acid derivatives, of very low solubility, which crystallize upon cooling of hot dimethyl sulfoxide solutions. In addition, dimethylformamide and dimethylacetamide seem to react with some benzimidazoles under the conditions of these experiments. Therefore, the use

of these solvents has been avoided where possible.

2.2.2. Purification Techniques Leading To High Purity Materials

Several techniques have been investigated for obtaining hyper-pure benzimidazoles. Thus far, the best method has been sublimation in vacuo (usually repeated sublimations). Because of their unique thermal stability even the higher molecular weight compounds such as p,p'-bis-(2-naphthimidazolyl)biphenyl (sublimed at 450°C), and 1,3,5-tris-(2-benzimidazolyl)benzene (sublimed at 420°-430°C) have proven to be sublimable. As the impurities seem to be either decomposed by the high temperatures involved (into gaseous and/or tarry products) or do not sublime, two or three sublimations usually result in a product which exhibits greater purity than any of the materials obtained by other methods. In addition, this has been the only satisfactory method for assuring a solvent-free material and, as will be noted below, there is increasing evidence that many of the benzimidazoles form complexes with solvents such as methanol and water. Formic acid salts of benzimidazoles will also form.

Standard sublimation techniques have been used satisfactorily for the lower molecular weight compounds. However, for those compounds which are very high subliming and from which many of the impurities sublime first, it has been found that sublimation in a long tube through a temperature gradient will often cause the impurities to sublime preferentially to the coolest portions of the tube while the benzimidazole collects in the hotter portions.

Two or three sublimations of this type have thus far reduced the most recalcitrant benzimidazole to a crystalline mass of sharp melting point.

An attempt has been made to purify 1,3-bis-(2-benzimidazolyl)-benzene by adsorption chromatography utilizing a mixture of benzene and ethyl acetate as a solvent on a silica gel column. The results of this experiment indicated that a considerable improvement in the purity of this material can be achieved by this method. However, the comparative advantages of this technique require further evaluation.

In view of the highly polar nature of benzimidazoles and their ability to form both acid and basic salts, another technique for purification might be chromatography with ion exchange resins. Preliminary investigations in this area indicate that this could be a fruitful area for further investigation.

Zone refining seems to be a very sensible method for the purification of benzimidazoles with melting points below about 350°C, particularly since this is the technique employed to obtain hyper-pure inorganic compounds for electrical applications. First efforts in this direction, using a molten zone travelling from the bottom to the top of a glass-enclosed sample, resulted in breakage of the glass tube envelope by the expansion of the compound upon melting. Reversing the direction of zone travel resulted in the sublimation of the compound through the hot region, leading to a kind of fractional sublimation process; this led to some sweeping of the impurities to the bottom of the tube, but seemed to be accompanied by a gradual decomposition of

the compound. Intermediate results could be obtained by horizontal orientation of the apparatus, but with no perceptible improvement in performance.

It was also anticipated that vapor phase chromatography might offer a useful method either for the purification of benzimidazoles or for the determination of their purity. Since these compounds can generally be sublimed, it seems reasonable to suppose that some sufficiently inert column packing, run at a sufficiently high temperature, would pass, and perhaps resolve, various compounds of this type. In fact, no such conditions could be found even when a short column was packed with pure sand and run at 300°C.

3. COMPARISON OF PHYSICAL PROPERTIES

The properties of the benzimidazoles synthesized in the course of this project show several consistent patterns. Infrared absorption spectra and ultraviolet absorption spectra have been taken on these compounds, and rough comparisons of their solubilities, melting points, flourescent properties have been made. Preliminary conductivity measurements are being used as criteria for purity.

3.1 Infrared Spectra

Infrared spectra of this series of compounds are all consistent with the benzimidazole structure. Several useful correlations can be applied to further compounds of this class. A pair of absorption bands, probably due to the -C=N vibration, are found at 6.2 and 6.3 microns. These bands may be weak and one may be a shoulder. A strong absorption band at 7.60 - 7.66 microns, probably due to the phenyl-nitrogen stretching vibrations is always present, but may often be a shoulder of an adjacent stronger band. The N - H stretching absorption at about 2.9 microns in the spectra of 2-alkylbenzimidazoles in solution is not evident in spectra of the solid state.[8] However, this band is seen in the spectra of many of the solid state phenyl substituted compounds.

The entire series has an aromatic C=C peak at 6.90 - 7.00 microns. (Unsubstituted benzimidazole has two peaks at 6.85 and 7.10 microns in this region.) Further, aromatic absorption bands are found at 7.85 - 7.90 microns and at 8.13 - 8.18 microns.

The former band is very weak in the 2-phenyl-substituted compound and is missing in 2-trifluoromethylbenzimidazole. The latter band is found in all compounds of this series except those having nitro or chloro substituents on the benzene ring of the benzimidazole. Several other correlations due to the nature of the aromatic substitution may be found within a particular group of this series. For example, the di- and tribenzimidazoles linked through the 2-position by a benzene ring all have a very strong band at 6.97 - 7.00 microns with a shoulder at 6.85 - 6.90 microns and a moderately strong band at 7.82 microns. The stronger band is not found within this range for any other compound of the series. Many other similarly limited correlations can be made.

3.2. Ultraviolet Spectra

Table I lists the wavelength and normal extinction coefficients (based on benzimidazole residues) for the first three ultraviolet absorption maxima observed below 400 mμ in tetrahydrofuran or methanol. These generally occur in the form of a right-hand and left-hand shoulder on a principle central peak. Where only one broad absorption is found, it is listed as the central peak. It is interesting to note the smooth shift to longer wavelengths with increasing conjugation. This series gives the first quantitative indication of the relative properties of these compounds; particularly interesting are compounds 6 and 9, the cross-conjugated dimer and trimer, which are not far removed in their spectral properties from their prototype 2-phenyl-benzimidazole. Contrast this with

the large shift to longer wavelengths seen in compound 17, the highly conjugated para-dimer. Also noted should be the large increase in the ultraviolet absorption associated with aromatic substituents, as compared with aliphatic. The listed extinction coefficients must be treated as approximate, since no corrections for fluorescence or overlap have been made.

TABLE I ULTRAVIOLET ABSORPTION DATA

	λ_1*	ϵ_1†	λ_2	ϵ_2	λ_3	ϵ_3
I. Aromatic or Olefinic Substituents:						
1. 2-Phenylbenzimidazole	296	17	304	19	317	16
2. 2-o-Tolylbenzimidazole	295	30	304	16	319	3
3. 2-m-Tolylbenzimidazole	297	11	305	13	319	8
4. 2-p-Tolylbenzimidazole	298	14	306	17	320	10
5. 2-m-Tolyl-5-methylbenzimidazole	300	24	307	23	323	13
6. 1,3-Bis(2-benzimidazolyl)benzene	300	15	309	19	322	12
7. 2-Phenyl-5-chlorobenzimidazole	301	20	309	23	323	18
8. 2-Phenyl-5-methylbenzimidazole	301	16	310	19	323	13
9. 1,3,5-Tris(2-benzimidazolyl)benzene	302	13	314	18	327	13
10. 1,3-Bis(5-methyl-2-benzimidazolyl)benzene	306	13	314	16	328	11
11. 2-α-Naphthylbenzimidazole			318	12		
12. 2-β-Naphthylbenzimidazole	306	16	319	21	336	13
13. Poly-2,2'-(m-phenylene)-5,5'-bibenzimidazole			326			
14. 2,2'-Diphenyl-5,5'-bibenzimidazole			327			
15. 2-Styrylbenzimidazole	326	22	336	24	354	12
16. 2,2'-Di-β-naphthyl-5,5'-bibenzimidazole			340			
17. 1,4-Bis(2-benzimidazolyl)benzene	328		341		361	
18. β,β'-Bis(2-benzimidazolyl)-1,4-divinylbenzene	366		380		400	
II. Non-conjugating Substituents:						
1. Benzimidazole	268	1.8	273	2.6	280	3.0
2. 2-t-Butylbenzimidazole	271	3.2	275	4.5	282	4.9
3. 2-Trifluoromethylbenzimidazole	269	3.1	277	3.8	285	3.2
III. Anomolous Compounds:						
1. 2-Methyl-4-nitrobenzimidazole			325	6.4		
2. 2-Phenyl-4-nitrobenzimidazole	263	13	330	8.6	367	9.5

* Wavelengths are in millimicrons

† Extinction Coefficients in 10^3 Lcm^{-1} $eq\ wt^{-1}$

3.3 Qualitative Fluorescence

Many of the benzimidazoles, particularly those substituted with aromatic groups in the 2-position are fluorescent in the solid state. In many cases the solutions of such compounds are also fluorescent. Preparative to a more sophisticated evaluation a very rough qualitative analysis of their relative fluorescent behavior has been made by visual observation under ultraviolet light. The compounds dissolved in methanol (4 millimoles to 16 ml of methanol) were visually observed for fluorescence as neutral, acid and basic solutions under ultraviolet light. The results of this experiment are reported in Table II. In cases where the benzimidazoles would not dissolve at the above concentration, a saturated solution was used, and these are indicated by an asterisk in the table. The order of fluorescence is reported as the relative intensities which are indicated as 0 - not visibly fluorescent through 7 - very intense. Fluorescence was also observed for the same materials in their various crystalline states and the results are recorded in Table III.

In general, the materials with 2 or more benzimidazole groups and those compounds exhibiting greater conjugation show the greater fluorescence both in the crystalline state and in solution. The one exception is 1,3,5-tris-(2-benzimidazolyl)-benzene which does not fluoresce very intensely. The most highly fluorescent material synthesized in this laboratory is the highly conjugated β,β'-bis-(2-benzimidazolyl)-1,4-divinyl-benzene followed in intensity by the other dimers, 2-styryl-

TABLE II QUALITATIVE FLUORESCENT OBSERVATIONS
(in Methanol Solutions)

COMPOUNDS	NEUTRAL†		ACID†		BASIC†	
	Color	Relative Intensity	Color	Relative Intensity	Color	Relative Intensity
β,β'-Bis-(2-benzimidazolyl)-1,4-divinylbenzene*	blue	7	yellow	7	blue-white	7
2,2'-Di-β-naphthyl-5,5'-bibenzimidazole*	blue	7	white	7	blue-white	7
1,4-Bis-(2-benzimidazolyl) benzene*	blue	7	blue-white	7	blue-white	7
1,3,-Bis-(2-benzimidazolyl) benzene	blue-violet	5	blue	7	blue	6
1,3-Bis-(5-methyl-2-benzimidazolyl)-benzene	blue	5	blue-green	7	blue-white	5
2,2'-Diphenyl-5,5'-bibenzimidazole*	blue	4	green	6	blue-white	5
2-Styrylbenzimidazole	blue	4	violet	1	blue	6
2-α-Naphthylbenzimidazole	violet	3	blue	6	blue-white	6
2-m-Tolyl-5-methylbenzimidazole	blue	2	blue	2	violet	5
2-β-Naphthylbenzimidazole	blue	2	blue	5	blue	6
2-p-Tolylbenzimidazole	violet	1	blue	2	blue	2
2-Phenyl-5-methylbenzimidazole	violet	1	violet	2	violet	1
2-Phenyl-5-chlorobenzimidazole	violet	1	violet	1	violet	1
1,3,5-Tris-(2-benzimidazolyl)-benzene*	violet	1	green	4	green	3
2-m-Tolylbenzimidazole		0	violet	1		0
2-o-Tolylbenzimidazole		0	violet	1		0
Poly-2,2'-(m-phenylene)-5,5'--bibenzimidazole*		0		0		0
2-Methyl-4-nitrobenzimidazole		0		0		0
2-Phenyl-4-nitrobenzimidazole		0		0		0
2-Trifluoromethylbenzimidazole		0		0		0
2-t-Butylbenzimidazole		0		0		0

*These compounds are not soluble to the extent of 4 millimoles in 16 ml of methanol and the solutions used are saturated solutions.

†Relative intensity is rated from 7 - very fluorescent to 0 - not visibly fluorescent.

TABLE III QUALITATIVE FLUORESCENT OBSERVATIONS
(Crystalline State)

COMPOUNDS	PREPARATIVE TECHNIQUE	FLUORESCENCE
β,β'-Bis-(2-benzimidazolyl)-1,4-divinylbenzene	yellow powder from solution	bright yellow
2,2'-Di-β-naphthyl-5,5'-bibenzimidazole	1. powder from MeOH 2. sublimed yellow crystals	1. green 2. green
1,4-Bis-(2-benzimidazolyl)benzene	1. powder from DMSO 2. sublimed	1. pale yellow green 2. violet blue
1,3-Bis-(2-benzimidazolyl)benzene	1. white powder from MeOH (m.p. 177°C) 2. sublimed white crystals	1. pale violet 2. blue white
1,3-Bis-(5-methyl-2-benzimidazolyl)-benzene	1. from MeOH, cream powder 2. sublimed, colorless glass	1. pale yellow 2. blue violet
2,2'-Diphenyl-5,5'-bibenzimidazole	1. cream crystals from solution 2. sublimed cream crystals	1. bright green 2. white-violet
2-Styrylbenzimidazole	sublimed white crystals	pale blue violet
2-α-Naphthylbenzimidazole	1. white crystals from MeOH 2. white crystals sublimed	1. very pale red violet 2. very pale red violet
2-m-Tolyl-5-methylbenzimidazole	from MeOH, white beads	bright blue white
2-β-Naphthylbenzimidazole	sublimed white crystals	very pale red violet
2-p-Tolylbenzimidazole	sublimed white powder	blue
2-Phenyl-5-methylbenzimidazole	sublimed white crystals	very very pale blue
2-Phenyl-5-chlorobenzimidazole	sublimed white crystals	faint violet
1,3,5-Tris-(2-benzimidazolyl)-benzene	1. white powder from THF 2. sublimed white crystals	1. white 2. yellow green
2-m-Tolylbenzimidazole	sublimed white crystals	very very pale blue
2-o-Tolylbenzimidazole	sublimed white crystals	bright yellow (decomposes)
Poly-2,2'-(m-phenylene)-5,5'--bibenzimidazole	yellow powder from melt	yellow
2-Methyl-4-nitrobenzimidazole	yellow crystals from solution	not fluorescent
2-Phenyl-4-nitrobenzimidazole	sublimed yellow powder	yellow
2-Phenylbenzimidazole	1. from EtOH cream powder 2. sublimed white crystals	1. violet red 2. blue
2-Trifluoromethylbenzimidazole	1. sublimed white crystals 2. white powder from water	1. blue 2. blue
2-t-Butylbenzimidazole	sublimed white crystals	faint white

benzimidazole and the two naphthylbenzimidazoles. Almost without exception, either the acid or the basic solution or both are considerably more fluorescent than the neutral solution. However, there is often very little correlation between fluorescence in the crystalline state and in acid, basic, or neutral solution. The color of the fluorescence for a given compound varies depending on whether it is in acid, basic, or neutral solution or is a precipitated or sublimed sample in the solid state. One anomolous compound is 2-m-tolyl-5-methylbenzimidazole. This compound shows an unusually high degree of fluorescence in basic solution and also in the solid state (probably as the monohydrochloride). The sterically hindered 2-o-tolylbenzimidazole is unusually fluorescent in the crystalline state but loses this behavior in solution.

3.4 Stability

The benzimidazoles as a group are unusually stable both thermally and chemically. Decomposition temperatures above 450°C are not uncommon. The sterically hindered 2-α-naphthylbenzimidazole and 2-o-tolylbenzimidazole, however, tend to decompose under strong ultraviolet light. The 2-m-tolyl-5-methylbenzimidazole, the m-phenylene dimers, 1,3,5-trimer also show less thermal stability than other compounds of similar structure.

3.5. Crystal Properties

In the course of the experimental work many qualitative observations have been made concerning the relative solubilities,

melting points, and the ease of crystal formation of the various benzimidazoles. In general, the solubilities of the more symmetrical compounds are much lower and their melting points are much higher.

Benzimidazoles have high melting points and are generally crystalline materials when precipitated or sublimed. However, asymmetric substituents such as 5-substitution on the benzimidazole ring or o-or m-substituents on the 2-phenyl ring reduce the melting points.

The same asymmetric substitutions make crystallization difficult. The m-phenylene dimers tend to form glasses on sublimation rather than crystalline products although the 1,3-bis-(2-benzimidazolyl)benzene has been sublimed to a microcrystalline powder.

Solvent complexes appear to be formed with many of the asymmetric compounds. The compound which has been most thoroughly studied in this respect is 1,3-bis-(2-benzimidazolyl)benzene. This compound exhibits two distinct melting points. When precipitated from methanol-water it melts at 180°C and resolidifies at 260°C followed by melting at 308-310°C. Elemental analysis of this precipitate corresponds to a 1:1 water complex. Sublimed samples of this material melt at 308-310°C directly. Bands also appear in the infrared spectra of the potentially solvated compounds which are not present in the spectra of their sublimed samples.

3.6 Preliminary Conductivity Measurements

Preliminary conductivity data has been obtained on a limited series of benzimidazoles. Dark conduction, fitted to the equation $\sigma = \sigma_0 \exp(-E/kt)$, yields consistent values of E in the expected range.[9] While most of the data was obtained on highly purified samples, comparison of the conductivity of samples after further stages of purification are necessary in order to confirm that the data represents intrinsic conductivities. Comparison of E for 2-p-tolylbenzimidazole in the impure (E=0.83 e.v.) and the pure (E=1.3 e.v.) states demonstrates that such measurements, as expected, are necessary for monitoring the purity of these benzimidazoles. The value of E(1.4 e.v.) for pure 2-m-tolylbenzimidazole is similar to that for the pure 2-p-tolylbenzimidazole. A sample of 2-β-naphthylbenzimidazole, on the other hand, showed an E value of 0.57 e.v. and a conductivity about 10 times that of the 2-tolyl compounds. The conductivity data, however, because of the varying nature of the samples used, are only approximate and will probably require revision when the current series of measurements on a standardized sample form are completed. For this reason conductivity values are not included in this report. The E values, however are less sensitive to the nature of the sample. Although measurements on single crystals are preferred for the determination of conductivity and activation energy of pure compounds, the technique is impractical for monitoring successive stages of purification. Initial

measurements were made on pressed microcrystalline pellets. The final sample form chosen was a thin crystalline layer prepared by melting the compound between plates of conducting glass separated by Teflon spacers of 4×10^{-3}cm. thickness. The melt, when allowed to cool slowly forms a multi-crystalline film, the crystals of which appear continuous in the very short current path. This technique conveniently allows one to vary the degree of crystallinity of the sample in order to determine whether the measured conductivity is independent of sample preparation. Such a procedure is difficult with pressed powders.

Since the measurements are currently being made with D.C. apparatus shown in Figure 1, they are sensitive to an initial rapid drop in conductivity due to polarization effects. Plots of current versus time following voltage application are similar to those of Riehl who reported the initial drop to be more rapid, the higher the conductivity and the temperature.[10] Current measurements are being taken at a 30 second interval after voltage application and yield linear plots of log conductivity vs 1/T over the temperature range studied as shown in Figure 2. Modifications are being made which will allow for measurements over a much broader temperature range. In addition the apparatus is being adapted for the study of pulse photoconduction.

Fig. 1 Conductivity cell used for electrical measurements. In the cell at left is a pressed pellet. At the right bottom is a sample between conducting glass plates.

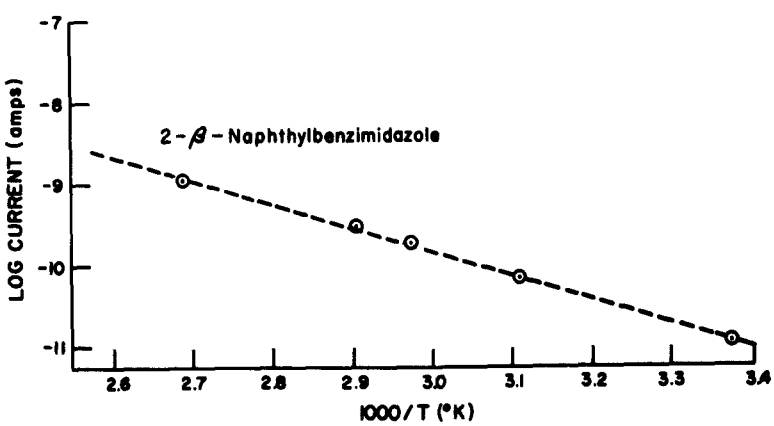


Fig. 2 Typical curve: temperature dependence of electrical conductivity

4. EXPERIMENTAL

4.1. Synthetic Procedures

Most of the compounds synthesized for this project were prepared by either the polyphosphoric acid method or one of the four melt condensation procedures. The remaining two were prepared by condensation of the appropriate aldehydes with 2-methylbenzimidazole. Descriptions of these procedures follow a discussion of the purification of starting materials. The objective of these syntheses has been to obtain high purity products rather than high yields. The data on the preparation of the compounds is summarized in Table IV. Infrared and ultraviolet spectra in all cases are consistent with the assumed structures.

4.1.1. Preparation and Purification of Starting Materials

The carboxylic acids used were all commercially available and when necessary were recrystallized from methanol before use. Commercial phenyl esters were recrystallized from methanol-water as necessary, and those not commercially available were prepared from the acid chlorides by standard techniques. Those acid chlorides not commercially available were made by the reaction of the acids with thionyl chloride.

o-Phenylenediamine and 3,4-diaminotoluene are commercially available from Distillation Products Industries of Eastman Kodak Company and were purified before use by the procedure described in Organic Syntheses.[11]

The 3,3'-diaminobenzidine tetrahydrochloride was obtained from two suppliers, Aldrich Chemical Co. and Burdick and Jackson Laboratories. Both materials were used directly in the form of

TABLE IV SUMMARY CHART OF BENZIMIDAZOLES

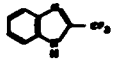
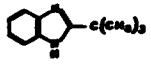
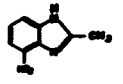
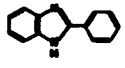
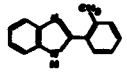
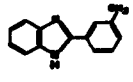
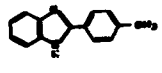
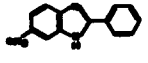
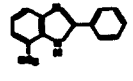
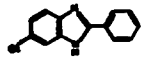
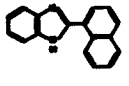
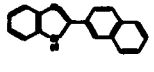
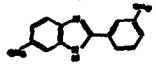
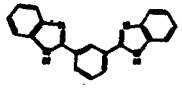
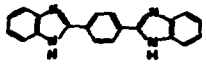
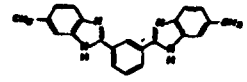
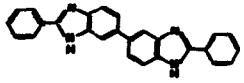
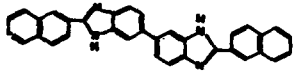
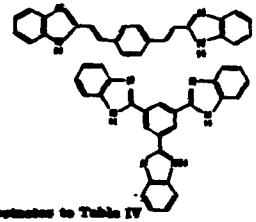
Compound[a]	Mol. Wt.	Reference Number	Synthetic Method	Quantities of Reactants in Moles		Crude Yield %	M.P.°C Uncorrected (M.P. Lit.)	Analytical Data			
				Acid/Ester	Amine			Found (Theoret.) C	Found (Theoret.) H	Found (Theoret.) N	Found (Theoret.) Other
	186	14,9(IR)	4.1.3.3	0.134	0.046	ca. 80	210-211 (210-210.5)	51.67 (51.62)	2.80 (2.71)	15.15 (15.05)	——— (30.62) (Fluorine)
	174	13	4.1.3.3	0.098	0.046	ca. 10	320-325[b] (315)	75.4 (75.8)	7.98 (8.09)	16.5 (16.1)	———
	177	12	4.1.3.3	0.073	1.000	75	222-223 (217-218)	50.52 (54.25)	4.04 (3.99)	23.84 (23.72)	18.10 (18.06) (Oxygen)
	194	3	4.1.2	0.1	0.1	ca. 80	294-297 (294)	——— (80.39)	——— (5.19)	——— (14.42)	———
	208	22 24(UV)	4.1.2	0.1	0.1	67	225-226 (223-224)	80.71 (80.74)	5.87 (5.81)	13.68 (13.45)	———
	208	3,15(m.p.) 24(UV)	4.1.2	0.1	0.1	80	219.5-221 (217-218)	(80.3) (80.74)	(5.84) (5.81)	(14.2) (13.45)	———
	208	23(m.p.),15 24(UV)	4.1.2 4.1.3.2	0.1 0.1	0.1 0.1	80 80	279-280 (271)	81.06 (80.74)	5.97 (5.81)	13.51 (13.45)	———
	208	20 24(UV)	4.1.2	0.1	0.1	80	246.5-248 (246)	80.55 (80.74)	5.92 (5.81)	13.67 (13.45)	———
	238	12,15(m.p.)	4.1.3.3 4.1.3.1	0.140 0.1	0.052 0.1	45 25	196-198 (194-195)	65.97 (65.57)	3.67 (3.78)	17.52 (17.57)	13.56 (13.58) (Oxygen)
	228	20	4.1.2	0.1	0.1	67	211-212 (210)	68.30 (68.28)	3.96 (3.97)	12.90 (12.25)	15.13 (15.50) (Chlorine)
	254	16	4.1.2 4.1.3.2[d]	0.1 0.05	0.1 0.05	48 66	269.5-270.5 (269-262)	83.3 (83.5)	4.83 (4.94)	11.9 (11.44)	———
	254	21	4.1.2	0.05	0.05	40	219-220.5 (215-216)	(83.6) 83.5	5.02 (4.94)	11.58 (11.44)	———
						30	301-302	81.89	5.32	12.46	———

TABLE IV SUMMARY CHART OF BENZIMIDAZOLES (CONTINUED)

Compound[a]	Mol. Wt.	Reference Number	Synthetic Method	Quantities of Reactants in Moles		Crude Yield %	M.P. °C Uncorrected (M.P. Lit.)	Analytical Data			
				Acid/Ester	Amine			Found (Theoret.) C	Found (Theoret.) H	Found (Theoret.) N	Found (Theoret.) Other
	222	None	4.1.3.1 4.1.3.2[d] 4.1.2	0.1 0.3 0.25	0.1 0.3 0.25	50 70 70	303-306[c] (———)	70.82 (81.05)	5.12 (5.36)	10.51 (12.60)	13.36[c] (?)
	310	None	4.1.2 4.1.3.1	0.066 0.1	0.133 0.2	50 90	308-310 (———)	77.57 (77.40)	4.48 (4.55)	17.87 (18.05)	
	310	18	4.1.2 4.1.3.1 4.1.3.4	0.1 0.1 0.1	0.3 0.2 0.2	low 25 60	473-475 (———)	77.55 (77.40)	4.52 (4.55)	17.82 (18.05)	
	338	None	4.1.3.1	0.05	0.1	low	Irreversible at 180 (———)	——— (78.06)	——— (5.36)	——— (16.56)	
	386	5	4.1.2[f]	0.1	0.05	low	420-422 (355)	81.07 (80.81)	4.77 (4.70)	14.56 (14.50)	
	487	None	4.1.3.2[g]	0.05	0.025	25	416-418 (———)	83.45 (83.93)	4.50 (4.56)	12.01 (11.52)	
	362	19	4.1.4	h	h	10	does not melt (———)	——— (79.53)	——— (5.01)	——— (15.46)	
	426	None	4.1.3.1[i]	0.05	0.15	66	454-456 (———)	78.20 (76.04)	4.24 (4.25)	19.68 (19.71)	

Footnotes to Table IV

a. All compounds have been triply sublimed and are white crystalline products unless otherwise indicated.

b. This compound sublimes above 250°C in air which makes taking the melting point difficult.

c. The analysis was made on a sublimed sample which had the above listed m.p. This analysis corresponds approximately to the benzimidazole monohydrochloride (C=69.9, H=5.8, N=10.85, Cl=13.7). A sample of the sublimed material gave positive tests for chlorine. When the sublimed material was reprecipitated from ammoniacal methanol it melted at 207°-209°C and no longer tested positively for chlorine.

d. The solvent for this reaction was phenol.

e. The reactants for this compound were 0.50 mole 2-methyl benzimidazole and 0.375 moles benzaldehyde.

f. This reaction utilized the tetrahydrochloride of 3,3'diaminobenzidine and the reaction mix foamed greatly in the initial stages of the preparation.

g. The tetrahydrochloride was used utilizing m-cresol as a solvent.

h. The reactants for this compound were 0.05 moles 2-methylbenzimidazole and 0.025 terephthalaldehyde.

i. The phenyl ester of trimesic acid was made from the acid chloride, which was also prepared in this laboratory. Indications are that neither reaction was complete but the reaction mixture-used directly as the triphenyl ester - proved a suitable starting material for the benzimidazole. No carbonyl bands appear in the infrared spectrum of the product.

the hydrochloride except in the preparation of poly-2,2'-(m-phenylene 5,5'-bibenzimidazole for which the tetrahydrochloride was converted to the free base and purified by the precedure used by Vogel and Marvel. [5]

The 1,2-diamino-3-nitrobenzene used in the preparation of 2-methyl-4-nitrobenzimidazole and 2-phenyl-4-nitrobenzimidazole was made by the method reported by Rabinowitz and Wagner with the substitution of methanol for the ethanol. [12]

Polyphosphoric acid is commercially available from the Victor Chemical Works and was used as supplied.

4.1.2. Polyphosphoric Acid Method

Stoichiometric quantities of o-phenylenediamine or a substituted o-phenylenediamine and the carboxylic acid were added to 250 ml of polyphosphoric acid in a 500 ml resin kettle. This viscous mixture was slowly heated with stirring and under nitrogen to 230°C (± 30°). The resulting solution was stirred at 230°C (± 30°) for three to four hours, permitting it to cool to about 100°C and poured in a thin stream into a rapidly stirred mixture of 1.5 liters of ice and water. The insoluble flocculent residue was collected by filtration, washed with a small amount of water and slurried with enough aqueous sodium hydroxide to give a pH of 9 to 10. After standing for a few minutes the alkaline slurry was filtered and the precipitate washed once with water. The product was then extracted from the precipitate with successive portions of hot methanol. After treatment of the combined alcoholic extracts totaling 300 to 1000 ml with a small amount of activated charcoal, hot water was added to the boiling

filtrate until crystallization was imminent. The product crystallized from the solution upon cooling and was collected by filtration.

4.1.3. Melt Condensation Methods

4.1.3.1. Phenyl Ester Reactions

Stoichiometric quantities of o-phenylenediamines and phenyl esters of carboxylic acids were normally used. After thoroughly mixing the two powders in the dry state a few drops of concentrated hydrochloric acid were added and the resulting mixture was heated under nitrogen to 250°to 290°C over a period of one hour and held at that temperature for one or two hours longer. The water and phenol evolved during the course of the reaction were condensed and collected. The reaction is terminated when most of the anticipated amount of phenol has been driven off. The remaining phenol can be removed by evacuation of the flask if desireable.

The product was isolated by leaching out the impurities with 6 to 8 small portions of methanol or methanol-ether (for the lower molecular weight products) or until a fairly light colored crystalline product was obtained.

In the case of 1,4-bis-(benzimidazolyl)benzene, the product was instead dissolved away from the impurities with 6 N aqueous sodium hydroxide and precipitated by the addition of concentrated hydrochloric acid.

4.1.3.2. Direct Aromatic Acid Synthesis

In this procedure stoichiometric quantities of o-phenylenediamines and the aromatic carboxylic acid were employed. In addition, a catalytic amount of hydrochloric acid was used and an

equimolar quantity of phenol or m-cresol - - with respect to the aromatic acid - was added as a solvent. The reactions were run and the products isolated in the same fashion as in the phenyl ester synthesis described above.

4.1.3.3. Direct Acid Synthesis

In this procedure o-phenylenediamines were reacted with an excess of liquid aliphatic acid and/or acid anhydride. The reaction was generally carried out at the reflux temperature of the acid or at 100°C for periods of from 4 to 8 hours. The mixture was then poured into cold aqueous sodium hydroxide, decolorized and neutralized with hydrochloric acid. The precipitate formed was collected, dried and recrystallized when necessary. When 4-nitro-o-phenylenediamine was used in this procedure it was necessary to employ a 2:1 acetic acid: acetic anhydride mixture in order to obtain satisfactory yields. Reaction of this amine with pure benzoic anhydride gave the corresponding 2-phenyl compound.

4.1.3.4. Methyl Ester Reactions

Stoichiometric quantities of o-phenylenediamines were mixed with the methyl ester of an aromatic carboxylic acid. In addition to the catalytic amount of hydrochloric acid, an equimolar quantity of phenol (with respect to the aromatic acid) was added as a solvent. The reactions were run and the products isolated in the same fashion as the product from the phenyl ester synthesis described above.

4.1.4. Aromatic Aldehyde Condensation

I. In this first method, 50 milli-equivalents of an aromatic aldehyde and 6.6 gm of 2-methylbenzimidazole are dissolved in

100 ml of triethyl phosphate. Direct use of commercial materials often yields a brown solution at this point; this should be decolorized with charcoal to a pale yellow. This solution is heated to reflux (216°C) for about two hours, cooled, and poured into 700 ml cold water. The resultant solution is made slightly acid with aqueous hydrochloric acid, and the precipitate filtered, washed, and recrystallized from a suitable solvent.

II. In the second method the above quantities of reactants are dissolved in 100 ml of an equi-volume mixture of acetic acid and acetic anhydride. This solution is refluxed, with gradual removal of solvent, over a period of three hours to a volume of about 40 ml. The solution is allowed to cool somewhat and enough water is added to destroy residual acetic anhydride. This solution is diluted with water to about 500 ml and made neutral with aqueous ammonia. The precipitate is collected and recrystallized as above.

The bright yellow β,β'-bis-(2-benzimidazolyl)-1,4-divinyl-benzene can be made from terephthalaldehyde by either of the above procedures, the first going in higher yield and the second leading to the better product. Only the second was successful in the preparation of 2-styrylbenzimidazole from benzaldehyde; here an excess of ammonia must be used to react with residual benzaldehyde, and care must be exercised in the isolation of the very soluble product. Some 2-methylbenzimidazole remains in the product and must be removed by sublimation.

4.2. Purification of Compounds

4.2.1. Sublimation at Moderate Temperatures

For sublimation at moderate temperatures a large sublimator

of essentially standard design was constructed (3.5 inch cylindrical chamber with a 2 inch air or water cooled probe). This has proven satisfactory for benzimidazoles melting below 300°C.

In general, the sublimator was loaded with about 2.5 g. of preliminarily purified benzimidazole. In the vacuum sublimation, it has been found that a suitable rate of sublimation can be obtained at 20°-30° below the melting point of most benzimidazoles. This method is unsuitable for compounds containing impurities which sublime or boil at a lower temperature than the benzimidazole and condense along with the benzimidazole on the probe (the case for most of the higher molecular weight materials).

Usually in the course of second and third sublimations no further colored decomposition products appeared in the bottom of the sublimator and very little residue remained. The sublimations were carried to completion. Three such sublimations normally constitute the final level of purification for these compounds.

4.2.2. Sublimations at Higher Temperatures

For those materials containing impurities which sublime or boil at lower temperatures than the benzimidazole and for those benzimidazoles of exceptionally high melting or sublimation point, sublimation was conducted in a long, continuously evacuated pyrex tube. The lower 3.5-4 inches of the tube was immersed in a sand bath, heated from the bottom, which provided a temperature gradient in the bath of about 200°C for the normal sublimation temperature of 400-450°C at the lower end of the tube.

Samples of 1 gram or less were placed in lipless pyrex test tubes of about 3 inches length which fitted quite closely in the long tube. Under these conditions the more volatile impurities normally sublime out of the inner tube and the removal of the sublimed sample is also facilitated. Repeated sublimations were usually accompanied by little or no residue or colored decomposition products. Three such sublimations normally constitute a purified product.

4.2.3. Adsorption Chromatography

Into 100 ml of refluxing ethyl acetate one gram of impure 1,3-bis-(2-benzimidazolyl)benzene was introduced. Solution was facilitated by the addition of acetone which was boiled off after the addition of 100 ml of benzene. Enough benzene was added to bring the volume of the solution up to 300 - 350 ml. The hot solution was put on 60 g of silica gel (Grade 923, 100 - 200 mesh, Davison Chemical Company). The charge was washed onto the columnwith 200 ml of 25% ethyl acetate in benzene. The position of the benzimidazole on the column was followed under fluorescent light, and when the violet fluorescent band had moved away from the top of the column leaving a small yellow non-fluorescent band at the top, it was eluted with 50% ethyl acetate: benzene. Fractions of about 33 ml were taken and dried at 80 - 100°C in a stream of nitrogen and weighed. Of the 36 fractions taken, numbers 4 to 21 of the yellowish crystals were combined, recrystallized from methanol and air-dried to yield 440 mg. fine white crystals. The purity of this material is greater than that of the starting material, but it is doubtful whether it is as good as the sublimed material.

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